

(19) 世界知的所有権機関 国際事務局



(43) 国際公開日 2004年5月21日(21.05.2004)

PCT

(10) 国際公開番号 WO 2004/041320 A1

(51) 国際特許分類7:

A61L 27/46, 27/56, 27/58

(21) 国際出願番号:

PCT/JP2003/013717

(22) 国際出願日:

2003年10月27日(27.10.2003)

(25) 国際出願の言語:

日本語

(26) 国際公開の言語:

日本語

(30) 優先権データ:

特願2002-322507 2002年11月6日(06.11.2002) JP

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- (81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) 指定国(広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:

- 国際調査報告書

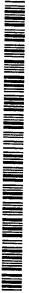
2文字コード及び他の略語については、定期発行される 各PCTガゼットの巻頭に掲載されている「コードと略語 のガイダンスノート」を参照。

(54) Title: APATITE/COLLAGEN CROSSLINKED POROUS MATERIAL CONTAINING SELF-ORGANIZED APATITE/COLLAGEN COMPOSITE AND PROCESS FOR PRODUCING THE SAME

(54) 発明の名称: 自己組織化したアパタイト/コラーゲン複合体を含むアパタイト/コラーゲン架橋多孔体及びその製造方法

(57) Abstract: A process for producing an apatite/collagen crosslinked porous material, comprising gelling a dispersion containing an apatite/collagen composite and collagen, lyophylizing the gel to thereby obtain a porous body and crosslinking the collagen of the porous body; and an apatite/collagen crosslinked porous material produced by this process.

)(57) 要約: アパタイト/コラーゲン複合体とコラーゲンとを含む分散物をゲル化した後で凍結乾燥することにより ▶ 多孔質体とし、次いで多孔質体中のコラーゲンを架橋することによりアパタイト/コラーゲン架橋多孔体を製造す ▶ る方法、及びこの方法により得られたアパタイト/コラーゲン架橋多孔体。



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明 細 書

自己組織化したアパタイト/コラーゲン複合体を含むアパタイト/コラーゲン 架橋多孔体及びその製造方法

発明の分野

5 本発明はアパタイト/コラーゲン複合体を含み、人工骨材、細胞の足場材等 に用いるアパタイト/コラーゲン架橋多孔体、及びその製造方法に関する。

従来の技術

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アパタイトからなる人工骨は自家骨に対して優れた親和性を有するために、自家骨に直接結合することができる。そのため、近年アパタイトからなる人工骨の有用性が評価されるようになり、整形外科、脳神経外科、形成外科、口腔外科等を中心に臨床応用されている。しかしアパタイトのようなセラミックス系の人工骨の機械的特性及び生理的性質は、自家骨と全く同じ訳ではない。例えばアパタイトのみからなるいわゆるセラミックス系人工骨は、自家骨より硬くて脆い。また自家骨は吸収と再生という代謝を繰り返すのに対し、アパタイトからなる人工骨は生体内でほとんど溶解しないため、生体内に半永久的に残存する。このため残存した人工骨が、人工骨と自家骨との界面で自家骨を破壊し、骨折の原因となることが懸念される。

最近、アパタイト人工骨より自家骨の組成に近く、生体内で分解する人工骨についての研究が活発化し、種々の提案がなされている。例えば特表平11-513590 号は、ハイドロキシアパタイトにコラーゲン及び必要に応じてその他のバインダーが結合したネットワークを有するアパタイト/コラーゲン架橋多孔体を開示している。このアパタイト/コラーゲン架橋多孔体は生体分解性を有するので、アパタイト/コラーゲン架橋多孔体内に自家骨が形成されるとともに、アパタイト/コラーゲン架橋多孔体自身は体内に吸収される。そのため、このアパタイト/コラーゲン架橋多孔体は脊椎固定、骨欠損の補填、骨折修復及び、周欠損移植等に利用できる。しかし、このアパタイト/コラーゲン架橋多孔体はコラーゲンとアパタイトとの単なる混合物からなるものであり、アパタイトの C 軸がコラーゲン繊維に沿って配向した生体骨の構造を有してい

ない。さらにこのアパタイト/コラーゲン架橋多孔体は機械的強度が不十分である他、骨形成能に乏しいという問題もある。

発明の目的

5 従って本発明の目的は、生体骨と同じ機構で体内に吸収されるとともに高い 骨形成能を有し、人工骨等に使用できるアパタイト/コラーゲン架橋多孔体、 及びその製造方法を提供することである。

発明の開示

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- 10 上記目的に鑑み鋭意研究の結果、本発明者らは、アパタイト/コラーゲン複合体とコラーゲンとを含有する分散物を凍結乾燥することによりアパタイト/コラーゲン架橋多孔体を製造する場合に、凍結乾燥に先立って分散物をゲル化させると、得られるアパタイト/コラーゲン架橋多孔体は均一な組織とともに高強度を有することを発見し、本発明に想到した。
- 15 すなわち本発明のアパタイト/コラーゲン架橋多孔体の製造方法は、アパタイト/コラーゲン複合体とコラーゲンとを含む分散物を凍結乾燥することにより多孔質体とした後で、前記多孔質体中のコラーゲンを架橋するもので、分散物をゲル化した後に凍結乾燥することを特徴とする。
- 分散物中の前記アパタイト/コラーゲン複合体と前記コラーゲンとの配合比20 は質量基準で97/3~93/7であるのが好ましい。またアパタイト/コラーゲン複合体中のアパタイト/コラーゲンの配合比は質量基準で9/1~6/4であるのが好ましい。

分散物をゲル化させる方法としては、分散物の温度を $35\sim43$ $^{\circ}$ に保持するのが好ましく、またゲル化処理に先立って、分散物の pH を $6.8\sim7.6$ とし、イオン強度を $0.2\sim0.8$ とするのが好ましい。

アパタイト/コラーゲン複合体は長さ 0.01~1 mm の繊維状であるのが好ましい。またアパタイト/コラーゲン複合体は、アパタイトの C 軸がコラーゲン繊維に沿うように配向した構造を有するのが好ましい。さらにアパタイト/コラーゲン架橋多孔体も、アパタイトの C 軸がコラーゲン繊維に沿うように配向

した構造を有するのが好ましい。

本発明のアパタイト/コラーゲン架橋多孔体は上記方法のいずれかにより製造される。

5 発明を実施する最良の態様

[1] アパタイト/コラーゲン複合体の製造

本発明のアパタイト/コラーゲン架橋多孔体の製造方法は、アパタイト/コラーゲン複合体と、バインダーとなるコラーゲンとを出発物質とする。アパタイト/コラーゲン複合体は、ハイドロキシアパタイトとコラーゲンが自己組織化的に配向し、生体骨と同様の構造を有するのが好ましい。ここで「自己組織化」とは、コラーゲン繊維に沿って、アパタイト構造を有する水酸化リン酸カルシウム (ハイドロキシアパタイト) が生体骨特有の配向をしていること、すなわちハイドロキシアパタイトの C 軸がコラーゲン繊維に沿うように配向していることを意味する。

15 (1) 原料

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アパタイト/コラーゲン複合体は、コラーゲン、リン酸塩、及びカルシウム塩を原料として製造する。コラーゲンは特に限定されず、動物等から抽出したものを使用できる。なお由来する動物の種、組織部位、年齢等は特に限定されない。一般的には哺乳動物(例えばウシ、ブタ、ウマ、ウサギ、ネズミ等)や 鳥類 (例えばニワトリ等)の皮膚、骨、軟骨、腱、臓器等から得られるコラーゲンを使用できる。また魚類 (例えばタラ、ヒラメ、カレイ、サケ、マス、マグロ、サバ、タイ、イワシ、サメ等)の皮、骨、軟骨、ひれ、うろこ、臓器等から得られるコラーゲン様蛋白を使用してもよい。なおコラーゲンの抽出方法は特に限定されず、一般的な抽出方法を使用することができる。また動物組織からの抽出ではなく、遺伝子組み替え技術によって得られたコラーゲンを使用してもよい。

リン酸又はその塩(以下単に「リン酸(塩)」という)としては、リン酸、リン酸水素ニナトリウム、リン酸二水素ナトリウム、リン酸水素ニカリウム、リン酸二水素カリウム等が挙げられる。またカルシウム塩としては、例えば炭酸

カルシウム、酢酸カルシウム、水酸化カルシウム等が挙げられる。リン酸塩及 びカルシウム塩はそれぞれ均一な水溶液又は懸濁液の状態で添加するのが好ま しい。

使用するアパタイト原料(リン酸(塩)及びカルシウム塩)とコラーゲンとの質量比により、生成するアパタイト/コラーゲン複合体の繊維長を制御できる。このため使用するアパタイト原料とコラーゲンとの質量比は、目的とするアパタイト/コラーゲン複合体の組成比により適宜決定する。本発明の製造方法に使用するアパタイト/コラーゲン複合体中のアパタイト/コラーゲンの比率は9/1~6/4とするのが好ましく、例えば8/2とする。

10 (2) 溶液の調製

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まずリン酸(塩)水溶液及びカルシウム塩水溶液又は懸濁液を調製する。リン酸(塩)水溶液及びカルシウム塩水溶液又は懸濁液の濃度は、リン酸(塩)とカルシウム塩とが所望の配合比にあれば特に限定されないが、後述する滴下操作の都合上、リン酸(塩)水溶液の濃度を 15~240 mM、例えば 120 mM 程度とし、カルシウム塩水溶液又は懸濁液の濃度を 50~800 mM、例えば 400 mM 程度とすれば良い。コラーゲンは一般的にはリン酸水溶液の状態で、前述のリン酸(塩)水溶液に加える。コラーゲンのリン酸水溶液としては、コラーゲンの濃度が 0.1~1 質量%、例えば約 0.85 質量%、リン酸の濃度が 1~40 質量%、例えば 20 mM 程度のものを使用する。

20 (3) アパタイト/コラーゲン複合体の製造

添加すべきカルシウム塩水溶液又は懸濁液の量とほぼ同量の水を予め反応容器に入れ、40℃程度に加熱しておく。そこに、コラーゲンを含有するリン酸(塩)水溶液と、カルシウム塩水溶液又は懸濁液とを同時に滴下する。滴下条件を制御することにより、合成するアパタイト/コラーゲン複合体の繊維長を制御できる。滴下速度は1~60 ml/分、例えば30 ml/分程度とするのが好ましい。また攪拌速度は1~400 rpm、例えば200 rpm 程度とするのが好ましい。

反応溶液の pH は 8.9~9.1 に保つのが好ましい。カルシウムイオン及び/又はリン酸イオンの濃度が上記範囲を超えると、複合体の自己組織化が妨げられる。以上の滴下条件により、アパタイト/コラーゲン複合体の繊維長は、アパ

タイト/コラーゲン架橋多孔体の原料として好適な1mm 以下となる。またアパタイト/コラーゲン複合体は、自己組織化したものとなる。

滴下終了後、スラリー状となった水とアパタイト/コラーゲン複合体との混合物を凍結乾燥する。凍結乾燥は、-10 $^{\circ}$ 以下に凍結した状態で真空引きし、急速に乾燥させることにより行う。

- [2] アパタイト/コラーゲン架橋多孔体の製造
- (1) アパタイト/コラーゲン複合体を含む分散物の調製

アパタイト/コラーゲン複合体に水、リン酸水溶液等の液体を加えて撹拌し、ペースト状の分散物を調製する。液体の添加量は、アパタイト/コラーゲン複合体 100 体積%に対して、80~99 体積%とするのが好ましく、90~97 体積%とするのがより好ましい。製造するアパタイト/コラーゲン架橋多孔体の気孔率 P は分散物中のアパタイト/コラーゲン複合体と液体との体積比に依存し、下記式(1):

 $P = A/(A+B) \cdot \cdot \cdot (1),$

15 (ただし、A は分散物中のアパタイト/コラーゲン複合体の体積、B は分散物中の液体の体積を示す。)により表される。このため加える液体の量を制御することによりアパタイト/コラーゲン架橋多孔体の気孔率 P を制御することができる。液体を加えた後で分散物を撹拌することにより、繊維状のアパタイト/コラーゲン複合体が切断され繊維の長さの分布幅が大きくなるため、製造するアパタイト/コラーゲン架橋多孔体の強度が向上する。

複合体の分散物にバインダーとなるコラーゲンを加え、さらに撹拌する。コラーゲンの添加量は、アパタイト/コラーゲン複合体 100 質量%に対して、1~10 質量%とするのが好ましく、3~6 質量%とするのがより好ましい。複合体の場合と同様に、コラーゲンはリン酸水溶液の状態で加えるのが好ましい。

- 25 コラーゲンのリン酸水溶液の濃度等は特に限定されないが、実用的にはコラーゲンの濃度は約 0.85 質量%、リン酸の濃度は 20 mM 程度である。
 - (2) 分散物のゲル化

コラーゲンのリン酸(塩)水溶液の添加により、分散物は酸性となるので、pHが7程度となるまで水酸化ナトリウム溶液等のアルカリ溶液を加える。分散

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物のpHは6.8~7.6とするのが好ましく、7.0~7.4とするのがより好ましい。分散物のpHを6.8~7.6とすることにより、バインダーとして加えたコラーゲンが、後述するゲル化処理時にゼラチンに変性するのを防止することができる。分散物にリン酸バッファー生理食塩水 (PBS) の10倍程度の濃縮液を加えて撹拌し、イオン強度を0.2~0.8に調整する。より好ましいイオン強度は、PBSと同程度のイオン強度(0.8程度)である。分散物のイオン強度を大きくすることにより、バインダーとして加えたコラーゲンの繊維化を促進することができる。

分散物を成形型に入れた後、35~43℃の温度に保持することにより分散物を がル化させる。保持温度は35~40℃とするのがより好ましい。分散物を十分に ゲル化させるため、保持する時間は0.5~3.5 時間とするのが好ましく、1~3 時間とするのがより好ましい。分散物の温度を35~43℃に保持することにより、 バインダーとして加えたコラーゲンが繊維化し、分散物がゲル状となる。分散 物がゲル化することにより、アパタイト/コラーゲン複合体が分散物中で沈降 するのを防ぐことができるため、均一な多孔質体を製造することが可能となる。 ゲル化処理を施した分散物はゼリー状となる。

(3) 凍結乾燥

ゲル化処理後の分散物を凍結する。凍結温度は-80~-10℃とするのが好ましく、-80~-20℃とするのがより好ましい。凍結速度により、多孔質体の気 20 孔径及び気孔形状を制御することができる。例えば凍結速度が大きいと、生成 する多孔質体の気孔径は小さくなる傾向がある。

次いで分散物を凍結乾燥して多孔質体とする。凍結乾燥は複合体の場合と同様に、-10℃以下に凍結した状態で真空引きし、急速に乾燥させることにより行う。凍結乾燥は分散物が十分に乾燥するまで行えばよく時間は特に制限されないが、一般的には 24~72 時間程度である。

(4) コラーゲンの架橋

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コラーゲンの架橋はγ線、紫外線、電子線、熱脱水等を用いた物理的架橋、 架橋剤や縮合剤を用いた化学的架橋等いずれの方法を用いてもよい。化学的架 橋の場合、架橋剤の溶液に凍結乾燥した多孔質体を浸すことにより、多孔質体 (

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中のコラーゲンを架橋する。

架橋剤としては、例えばグルタールアルデヒド、ホルムアルデヒド等のアルデヒド系架橋剤、ヘキサメチレンジイソシアネート等のイソシアネート系架橋剤、1・エチル・3・(3・ジメチルアミノプロピル)カルボジイミド塩酸塩等のカルボジイミド系架橋剤、エチレングリコールジエチルエーテル等のエポキシ系架橋剤、トランスグルタミナーゼ等が挙げられる。これらの架橋剤のうち、架橋度の制御の容易さや、得られるアパタイト/コラーゲン架橋多孔体の生体適合性の観点から、グルタールアルデヒドが特に好ましい。

架橋剤としてグルタールアルデヒドを用いる場合、グルタールアルデヒド溶 液の濃度は 0.005~0.015 質量%とするのが好ましく、0.005~0.01 質量%とするのがより好ましい。アパタイト/コラーゲン架橋多孔体は脱水する必要があるが、ここでグルタールアルデヒド溶液の溶媒としてエタノール等のアルコールを使用すると、アパタイト/コラーゲン架橋多孔体の脱水をコラーゲンの架橋と同時に行うことができる。脱水を架橋と同時に行うことにより、アパタイト/コラーゲン複合体が収縮した状態で架橋反応が起こり、生成するアパタイト/コラーゲン架橋多孔体の弾性を向上させることができる。

架橋処理後、未反応のグルタールアルデヒドを除去するため2質量%程度のグリシン水溶液にアパタイト/コラーゲン架橋多孔体を浸漬し、次いで水洗する。さらにエタノールに浸漬することによりアパタイト/コラーゲン架橋多孔体を脱水した後、室温で乾燥させる。

[3] アパタイト/コラーゲン架橋多孔体の物性及び用途

本発明のアパタイト/コラーゲン架橋多孔体は、自己組織化したアパタイト/コラーゲン複合体を含んでおり、従来のアパタイトアパタイト/コラーゲン 架橋多孔体より吸水性及び弾性が高い。また含水状態で弾力性を示し、優れた 生体親和性及び骨伝導能を有する。

上述のような物性は、生体材料として好ましい。このため本発明のアパタイト/コラーゲン架橋多孔体はγ線、電子線、乾燥加熱等により滅菌処理すると、生体骨置換型骨再建材等として使用できる。具体的には人工骨、人工関節、腱と骨との接合材、歯科用インプラント材等として好適である。

本発明を以下の実施例によってさらに詳細に説明するが、本発明はそれらに限定されるものではない。

実施例1

5 (A) アパタイト/コラーゲン複合体の合成

120 mM のリン酸水溶液 168 ml に、コラーゲンのリン酸水溶液(コラーゲン 濃度:0.85 質量%、リン酸濃度:20 mM)を 235 g 加えて撹拌し、希釈コラーゲンリン酸水溶液を調製した。他方、400 mM の水酸化カルシウム懸濁液を 200 ml 調製した。反応容器に 200 ml の純水を入れ、40℃に加熱した。この反応容 器に希釈コラーゲンリン酸水溶液と水酸化カルシウム懸濁液とをそれぞれ約 30 ml/分の速度で同時に滴下し、得られた反応溶液を 200 rpm で撹拌して、アパタイト/コラーゲン複合体繊維を含むスラリーを作製した。滴下中の反応溶液の pH は 8.9~9.1 に保持した。生成したアパタイト/コラーゲン複合体の繊維長は概ね 1 mm 以下であった。アパタイト/コラーゲン複合体を含むスラリーは 凍結乾燥した。アパタイト/コラーゲン複合体中のアパタイト/コラーゲンの配合比は、質量基準で8/2であった。

(B) アパタイト/コラーゲン架橋多孔体の作製

凍結乾燥したアパタイト/コラーゲン複合体 1 g に純水 3.6 ml を加えて撹拌し、ペースト状の分散物とした。このペースト状分散物にコラーゲンのリン酸 水溶液 4 g を加えて撹拌した後、1 N の NaOH 水溶液を pH がほぼ 7 になるまで加えた。アパタイト/コラーゲン複合体とコラーゲンとの配合比は質量基準で 97/3 であった。次いで分散物のイオン強度が 0.8 となるまで、10 倍濃縮の PBS を加えた。液体(純水+希釈コラーゲンリン酸水溶液+NaOH 水溶液+PBS)の添加量は、アパタイト/コラーゲン複合体の 95 体積%であった。

25 得られた分散物を成形型に入れ、37℃で 2 時間保持してゲル化させることにより、ゼリー状の成形体を得た。この成形体を一20℃で凍結し、次いで凍結乾燥機を用いて乾燥させた。エタノール(濃度 99.5%)を溶媒とする 0.01 質量%のグルタールアルデヒド溶液に乾燥した成形体を浸し、25℃で 1 時間架橋処理することにより、アパタイト/コラーゲン架橋多孔体を得た。このアパタイト

/コラーゲン架橋多孔体を水洗した後、2質量%のグリシン水溶液に浸して未 反応のグルタールアルデヒドを除去し、再度水洗した。さらにエタノール (濃 度 99.5%) に浸して脱水した後、室温で乾燥した。

得られたアパタイト/コラーゲン架橋多孔体から角柱状(5 mm×5 mm×10 mm)の試験片を切り出し、引張り速度を 0.1 mm/秒として破断強さを測定した。その結果、アパタイト/コラーゲン架橋多孔体の破断強さは約 0.8 N であった。

実施例2

10 ゲル化処理温度を 40℃とした以外実施例 1 と同様にしてアパタイト/コラーゲン架橋多孔体を製造し、破断強さを測定した。破断強さは約 0.8 N であった。

比較例1

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ゲル化処理を行わない以外実施例1と同様にしてアパタイト/コラーゲン架 15 橋多孔体を製造し、破断強さを測定した。破断強さは約0.4 N であった。

産業上の利用可能性

以上詳述したように、本発明の方法により、自己組織化したアパタイト/コラーゲン複合体を含むことにより優れた生体親和性及び骨伝導能を有し、破断20 強さ等の機械的強度が大きいアパタイト/コラーゲン架橋多孔体を製造することができる。このような特性を有するアパタイト/コラーゲン架橋多孔体は人工骨、人工関節等の生体材料として好適である。

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請求の範囲

- 1. アパタイト/コラーゲン複合体とコラーゲンとを含む分散物を凍結乾燥することにより多孔質体とした後で、前記多孔質体中のコラーゲンを架橋するこ
- 5 とによりアパタイト/コラーゲン架橋多孔体を製造する方法において、前記分 散物をゲル化した後に凍結乾燥することを特徴とする方法。
 - 2. 請求項1に記載のアパタイト/コラーゲン架橋多孔体の製造方法において、 前記アパタイト/コラーゲン複合体は、コラーゲンを含有するリン酸又はその 塩の水溶液と、カルシウム塩の水溶液又は懸濁液とを同時に滴下することによ り製造することを特徴とする方法。
 - 3. 請求項1又は2に記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記分散物中の前記アパタイト/コラーゲン複合体と前記コラーゲンとの配合比が質量基準で97/3~93/7であることを特徴とする方法。
- 4. 請求項1~3 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製 15 造方法において、前記アパタイト/コラーゲン複合体中のアパタイト/コラー ゲンの配合比が質量基準で9/1~6/4であることを特徴とする方法。
 - 5. 請求項 1~4 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記分散物をゲル化するために、前記分散物を 35~43℃の温度に保持することを特徴とする方法。
- 20 6. 請求項 $1\sim5$ のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記分散物の pH を $6.8\sim7.6$ とした後で前記分散物をゲル化することを特徴とする方法。
 - 7. 請求項 $1\sim6$ のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記分散物のイオン強度を $0.2\sim0.8$ とした後で前記分散物をゲル化することを特徴とする方法。
 - 8. 請求項1~7 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記アパタイト/コラーゲン複合体が長さ1mm 以下の繊維状であることを特徴とする方法。
 - 9. 請求項1~8 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製

造方法において、前記アパタイト/コラーゲン複合体中のアパタイトの C 軸が コラーゲン繊維に沿うように配向していることを特徴とする方法。

- 10. 請求項 1~9 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の製造方法において、前記アパタイト/コラーゲン架橋多孔体中のアパタイトの C 軸がコラーゲン繊維に沿うように配向していることを特徴とする方法。
- 11. 請求項 1~10 のいずれかに記載のアパタイト/コラーゲン架橋多孔体の 製造方法において、前記アパタイト/コラーゲン複合体中のアパタイトがハイ ドロキシアパタイトであることを特徴とする方法。
- 12. 請求項 1~11 のいずれかに記載の方法により製造されたアパタイト/コラ 10 ーゲン架橋多孔体。

INTERNATIONAL SEARCH REPORT

International application No.

A. CLASSIFICATION OF SUBJECT MATTER Int. C1 ⁷ A61L27/46, 27/56, 27/58 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELES SPARCHED Minimum documentation searched (classification system followed by classification symbols) Int. C1 ⁷ A61L27/46, 27/56, 27/58 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Jitsuyo Shinan Koho 1926-1996 Jitsuyo Shinan Toroku Koho 1994-2004 Kokai Jitsuyo Shinan Koho 1971-2004 Toroku Jitsuyo Shinan Koho 1994-2004 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS/MEDLINE/BIOSIS/EMBASE (STN) , JSTPlus/JMEDPlus (JOIS) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category Clation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Y WO 97/14376 A1 (ORQUEST, INC.) , 1-12 Calaims 11, 12 a AU 9675167 A a CN 1204245 A a E P S5584 A1 a JP 11-513590 A a NZ 321756 A a US 5776193 A Y JF 11-192081 A (Menicon Co., Ltd.), 21 July, 1999 (21.07.99), Par. No. [0015]; examples (Family: none) Y WO 01/92322 A1 (COLETICA), 06 December, 2001 (06.12.01), Examples a KR 2003010637 A a JP 2003-534858 A V JF 11-192081 A (COLETICA), 06 December, 2001 (06.12.01), Examples a KR 2003010637 A a JP 2003-534858 A V JF 11-192081 A (COLETICA), 06 December, 2001 (06.12.01), Examples a KR 2003010637 A a JP 2003-534858 A V JF Uniter documents are listed in the continuation of Box C.			ĺ	PCT/JP03/13717		
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